National Toxicology Program
Toxicity Report Series
Number 15

NTP Technical Report on Toxicity Studies of

t-Butyl Perbenzoate

(CAS NUMBER: 614-45-9)

Administered by Gavage to F344/N Rats and B6C3F$_1$ Mice

H.B. Matthews, PhD, Study Scientist
National Toxicology Program
Post Office Box 12233
Research Triangle Park, NC 27709

NIH Publication No. 92-3134
July 1992

United States Department of Health and Human Services
Public Health Service
National Institutes of Health

CONTRIBUTORS

The NTP report on the toxicity studies of t-butyl perbenzoate is based primarily on 14-day and 13-week studies performed over the period between March, 1985, and July, 1988, at Battelle Memorial Laboratories, Columbus, OH; and on disposition and stability studies performed at Research Triangle Institute, Research Triangle Park, NC.

National Toxicology Program
Evaluated experiment, interpreted results, and reported findings

H.B. Matthews, PhD
Study Scientist
John Bucher, PhD
Leo T. Burka, PhD
Michael Elwell, DVM, PhD
Joel Mahler, DVM
Morrow Thompson, DVM, PhD
Errol Zeiger, PhD

Coordinated Report Preparation

Jane Lambert, BS
Diane Overstreet, BS
Kristine Witt, MS
Oak Ridge Associated Universities

NTP Pathology Working Group
Evaluated slides and prepared pathology report

Katharina Heider, DVM
Chairperson
CIBA-GEIGY
Michael Elwell, DVM, PhD
National Toxicology Program
Jeffrey Everitt, DVM
CIIT
Joel Leininger, DVM, PhD
National Toxicology Program
Margarita McDonald, DVM, PhD
National Toxicology Program
John Peckham, DVM
Experimental Pathology Laboratories, Inc.

Battelle Columbus Laboratories
Principal contributors

Arthur C. Peters, DVM
Principal Investigator
M. Hejtmancik, PhD
Study Director, Toxicologist
Ming Chang, PhD
Chemistry
P. Jepsen, DVM, MS
Study Veterinarian
L. Mezza, DVM, MS
Pathology

Research Triangle Institute
Conducted disposition studies

Robert Jeffcoat, PhD
Principal Investigator
Monroe Wall, PhD
Co-Study Director
Thorir Bjornsson, PhD
Pharmacokinetics
Donald Feldman, DVM
Study Veterinarian
Timothy Tippin, BA
Chemist

Experimental Pathology Laboratories, Inc.
Provided pathology quality assurance

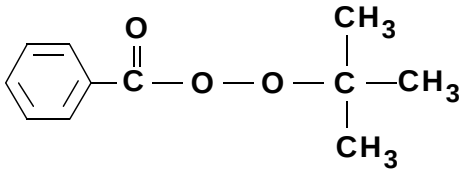
John Peckham, DVM

Analytical Sciences, Inc.
Provided statistical analysis

Richard Morris, MS
Steven Seilkop, MS
Janet Teague, MS

CONTENTS

t-BUTYL PERBENZOATE



Molecular Formula: $C_{11}H_{14}O_3$

CAS Number: 614-45-9

Molecular Weight: 194.25

Synonyms: Benzenecarboperoxoic acid; 1,1-dimethylester; Esperox 10; Trigonox C; t-BP.

ABSTRACT

t-Butyl perbenzoate (t-BP) is a relatively stable, lipid-soluble, organic peroxide widely used in the polymer industry. Studies were designed to determine the stability of t-BP in various biological media, its dermal absorption and distribution in intact animals, and the toxicity of t-BP when administered orally to both sexes of rats and mice for 14 days or 13 weeks. In genetic toxicity studies, t-BP was found to be mutagenic in *Salmonella typhimurium* strains TA100, TA1537, and TA98, with and without metabolic activation. t-BP-induced sister-chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells *in vitro* but did not induce formation of micronuclei in peripheral blood in mice in the 13-week studies.

Stability studies indicated t-BP was sufficiently stable in dose formulations to permit administration by gavage, intravenous injection, or dermally. However, t-BP degraded rapidly in blood, stomach contents, and liver homogenates, or in the presence of glutathione. Initial degradation products of t-BP are benzoic acid and t-butanol. Studies of t-BP disposition determined that approximately 16% of dermal doses administered to rats was absorbed and rapidly eliminated without tissue accumulation. Similarly, t-BP given intravenously was rapidly degraded and eliminated, primarily in urine, with no apparent accumulation in any tissue. Because dermal absorption was considered insufficient to administer a toxic dose, studies of t-BP toxicity were performed using gavage administration.

Results of 14-day toxicity studies with 5 animals of each sex of rats and mice indicated that t-BP, adminstered by gavage in corn oil in doses ranging from 70 to 1112 mg/kg, produced no marked signs of systemic toxicity. Toxicity in mice, attributable to t-BP, was limited largely to increased stomach weights in males and females receiving the highest doses. This toxicity was

characterized by forestomach epithelial hyperplasia, ulceration, and acute inflammation. Equimolar doses of the degradation products of t-BP (t-butanol and benzoic acid) also were administered in the 14-day studies to determine if t-BP toxicity could be attributed to the parent compound or products of its chemical degradation and/or metabolism. Results of these studies indicated that equimolar doses of t-butanol were not toxic in either sex or species. Some systemic toxicity of benzoic acid was observed in both sexes of mice, but not rats, receiving the highest dose (642 mg/kg). Toxicity was evidenced by the poor condition of dosed animals and in several deaths during the first week of the study. No lesions were observed microscopically, and it is speculated that this toxicity may have been due to acidosis.

In the 13-week studies, t-BP was administered by gavage in water to 10 rats and 10 mice of each sex, at doses up to 500 mg/kg. The doses resulted in depressed body-weight gains in the highest dose groups and in dose-dependent increases in forestomach weights. Hyperplasia of the forestomach mucosa was observed in most groups of dosed rats and increased in severity with dose. Hyperplasia was characterized by increased cellularity and basophilia of the squamous epithelium with variable degrees of hyperkeratosis. t-BP toxicity observed in mice was limited to increased forestomach weight in most dose groups and to less dramatic increases in glandular stomach weight in mice receiving the highest doses. Forestomach toxicity was characterized by dose-dependent increases in hyperplasia of the squamous epithelium in all mice except those in the low dose group.

Based on the results presented in this report, it is concluded that the no-observed-adverse-effect-level (NOAEL) for t-BP to induce forestomach lesions in rats and mice is approximately 30 mg/kg. Systemic toxicity was not observed in either species with oral doses as high as 1112 mg/kg.

PEER REVIEW

Peer Review Panel

The members of the Peer Review Panel who evaluated the draft report on the toxicity studies on t-butyl perbenzoate on March 11-12, 1991, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members act to determine if the design and conditions of the NTP studies were appropriate and to ensure that the toxicity study report presents the experimental results and conclusions fully and clearly.

National Toxicology Program's Board of Scientific Counselors Technical Reports Review Subcommittee

Paul T. Bailey, PhD
Mobil Oil Corporation
Toxicology Division
Princeton, NJ

Daniel S. Longnecker, MD, Chair
Department of Pathology
Dartmouth Medical School
Hanover, NH

Jay I. Goodman, PhD
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, MI

Ellen K. Silbergeld, PhD
University of Maryland Medical School
Baltimore, MD

Ad Hoc Subcommittee Panel of Experts

Louis S. Beliczky, MS, MPH
Department of Industrial Hygiene
United Rubber Workers Intl. Union
87 South High Street
Akron, OH

Gary P. Carlson, PhD
Department of Pharmacology and Toxicology
Purdue University
West Lafayette, IN

Harold Davis, DVM, PhD
School of Aerospace Medicine
Brooks Air Force Base, TX

Robert H. Garman, DVM
Consultants in Veterinary Pathology
Murrysville, PA

David W. Hayden, DVM, PhD
Department of Veterinary Pathobiology
College of Veterinary Medicine
University of Minnesota
St. Paul, MN

Curtis D. Klaassen, PhD
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Barbara McKnight, PhD
Department of Biostatistics
University of Washington
Seattle, WA

Lauren Zeise, PhD
California Department of Health Services
Berkeley, CA

Summary of Peer Review Comments

Dr. H.B. Matthews, NIEHS, NTP Staff Scientist, introduced the short-term toxicity studies of t-butyl perbenzoate (t-BP) by reviewing the uses of t-BP and the rationale for the study, findings from chemical disposition studies, experimental design, and results.

Dr. Hayden, a principal reviewer, said this was a well-documented and clearly written report indicating that t-BP had little or no toxicity to rodents other than changes in the stomach. He cautioned that on a long-term study there might be problems with stomach ulcers or perforating ulcers leading to excessive mortality.

Dr. Bailey, a second principal reviewer, also thought this was a well-performed study and a well-written report. He commented on an apparent contradiction in the draft report, that while the text states that t-BP is not "normally inhaled," it also cites reports of workers exposed to the chemical by inhaling t-BP vapors.

Dr. Davis asked whether the forestomach lesions were focused primarily around the limiting ridge as in some recent studies. Dr. M. Elwell, NIEHS, said that at the higher doses lesions were seen over large areas of the forestomach.

Dr. Carlson noted the disposition studies indicated significant amounts of radiolabel were found in skin taken from sites other than that used for dermal administration. Dr. Matthews indicated that this was a frequent finding in dermal disposition studies performed with volatile chemicals, and that it was not an artifact.

Following a short discussion of editorial and other comments, Dr. Longnecker indicated that the panel would accept the report, with the indicated changes.